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# Immunogenicity and Efficacy of the Hoshino Strain of Mumps (MMR Vaccine) in Iran

**M Avijgan[1]*, M Moghni[2], M Hafziz[2], S Kheiri[3], F Mirzadeh[1]**

*[1]Department of Infectious and Tropical Diseases, Iranian Traditional Medicine Research Centre, Isfahan*
*University of Medical Sciences, Isfahan, [2]Faculty of Medicine, Shahr-e-kord University of Medical*
*Sciences; [3]Department of Biostatistics and Epidemiology, Faculty of Health, Shahr-e-kord University of*
*Medical Sciences, Shahrekord, Iran*

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## Abstract

**Background:** Mumps is an infectious and common disease during childhood. The vaccination against some epidemic diseases like mumps has been introduced in national program. This report describes the immunogenicity and efficacy of Hoshino strain of mumps (included in MMR vaccine) in Iran during 2 years.
**Methods:** Three hundred and thirty eight children aged 3-18 years from Shahr-e-Kord, Iran were enrolled. They were tested for mumps IgG using enzyme-linked immunosorbent assay (ELISA). The percent of susceptible ***mumps IgG negative*** children was 19.8% (67 subjects), among them, 36 received the MMR vaccination and successfully completed the study. Blood sample was collected by venipuncture at 3, 12, and 24 months after vaccination and serum samples were tested by ELISA for detection of mumps IgM and IgG.
**Results:** The seroconversion rate was 86.1%, 77.7% and 75% at 3, 12, and 24 months after vaccination respectively.
**Conclusion:** Although the early serocoversion rate was high, but later it declined to a level of 75% which is the same immunity as natural infection which means that the immunity after vaccination would not last for long period of time and there may be a need for introduction of the booster dose of vacci

**Keywords:** Elisa; Hoshino strain; Immunogenicity; Mumps; Vaccine; Iran

***Correspondence:** Majid Avijgan, MD, Professor of Infectious and Tropical diseases, Iranian Traditional Medicine Research Centre, Al-Zahra Hospital, Isfahan University of Medical Sciences, P.O. Box: 597, Isfahan, Iran. e-mail: avijgan@yahoo.com
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## Introduction

As in many other developing countries, mumps was one of the causes of morbidity among children in Iran. In March 2004, mumps immunization was integrated in the expanded program of immunization (EPI) combined with measles and rubella (MMR).

Two previous studies carried out in Shiraz and Tehran in the Islamic Republic of Iran reported that 34.2% of the population in Shiraz study in southern Iran and 82.3% of 5-year-olds and 29.4% of 10-year olds in Tehran study were seronegative against mumps.[1,2] No other data on the community herd immunity against mumps or persistency of antibodies against Hoshino strain of mumps was available before this integration. Recently we conducted a study to determine the seroprevalence of mumps which indicated about 81.2% seropositivity against children aged 3-18 years in Shahr-e-Kord, Iran at 2004.[3] By considering the 18.8% seronegative children of general population and by integration of mumps vaccine in Iranian EPI and also no exact data on immunogenicity of Hoshino strain of mentioned mumps vaccine, for determining such obscure issue, (immunogenicity of Hoshino strain), we did a serial study. The main aim of these serial studies were to evaluate the immunogenicity, efficacy and long term immunity of the Hoshino strain of mumps

(included in MMR vaccine) against mumps in Shahr-e-Kord, Iran, during a period of 2 years after MMR vaccination in a group of seronegative susceptible children.

## Materials and Methods

From January 2004 to December 2006 by coducting a serial studies in a selected group of children in Shahre-Kord, Iran, 3-18 years old children were selected from 158 schools and 100 daycare centers by stratified random sampling method. The size of the sample in each stratum was taken in proportion to the size of the stratum**.** A sample size of 338 children aged 3-18 years old were enrolled (56.5% boys).[3] Data collection was based on an interview questionnaire and serology testing. The parents of selected children were given a formal invitation to attend the school where their consent to participation was obtained. We did not encounter any refusals and, with the cooperation of the manager of schools, all selected children participated in the study. The parents were interviewed by our co-investigator (a general practitioner) to collect data such as age, sex, history of previous exposure to mumps cases, history of previous mumps involvement and vaccination against mumps.

In the first part of study,[3] 67 seronegative children were included. These 67 seronegative children were invited for MMR vaccination. Only 44 children completed our second study (vaccination with present MMR vaccine in Iran) to evaluate the immunogenicity of mumps Hoshino strain of MMR vaccination. In the day of vaccination, a blood sample was collected and then they were injected by MMR vaccination (time 0), and were followed up 3 month (second part of study), 1 year (third part of study) and finally, at 2 years following vaccination (forth part of study) to find out the persistency of mumps antibodies. This means that blood specimens were collected on the day of vaccination (time 0) and then at 3, 12, and 24 months post-vaccination. Blood specimens were centrifuged and sera were stored in cryo-vials at -20$^0$C until all samples were tested simultaneously for mumps IgM and IgG (ELISA) kits manufactured by Trinity Biotech Capita, (Jamestown, USA, NY, 14701). All of them were tested simultaneously for IgG1 and IgM1 (at the day of vaccination), IgG2 and IgM2 (3 months), IgG3 and IgM3, (12 months) and IgG4 (24 months) following vaccination.

The quality control was done simultaneously with the measurement of samples. Based on the recommendation of the kit, negative and positive control numbers and the mean values were in an acceptable range. Based on the kit definition, the results were calculated as antigen–antibody ratios, and recorded as positive or negative.

Statistical analysis was performed based on using the SPSS software (version 11.5, Chicago, IL, USA). By using Fisher Exact and Cochran and Chi Square tests, *p* values less than 0.05 were considered statistically significant. Due to nearly 100% seronegativity of IgM3 (IgM3 means that the third time that we check the IgM) at the time of one year after vaccination, so the IgM4 (it means that IgM4 at the two years or last test) was ignored. Ethical approval for the study was obtained from the Ethical Committee of Shahr-e-Kord University of Medical Sciences, and referred to the local educational organization for approval.

## Results

This is a cross-sectional stratified random sampling study conducted in Shahr-e-Kord, Iran during between Jan 2004 to Dec 2006. This study included 338 children (M to F=1.3) aged 3-18 years who were tested for mumps IgG antibody by ELISA method.[3] Of 338 children screened, 67 (19.8%) were mumps IgG negative thus indicating that they were susceptible.

About 23% and 17.5% of girls and boys were mumps IgG negative respectively ($p$=0.226). Agespecific mumps IgG seroprevalence rose rapidly from 66.7% at age 7-11 years (primary schools) to 79.5% at age 12-14 years (guidance schools) and to 95.4% at age 15-18 years (high schools). Using $\chi 2$, there was a statistically significant difference between age and seroprevalence ($p$<0.001) (Table 1).

Forty four mumps IgG negative subjects (from 67 seronegative subjects in first part of study) accepted to be vaccinated with MMR vaccine to evaluate the immunogenicity of mumps Hoshino strain included in the MMR vaccine. From these 44 persons, forty children were present till the end of study, among them four (10%) subjects were excluded due to seroconversion (new infection). Therefore 36 children successfully completed the study. Based on age, this study

included two groups of children of 6-11 years old (20 persons) and 12-14 years old (16 persons). The seroconversion rate for 6-11 years old age group was 85% at 3 months. Mumps IgG was detected in 75% at 12 months and 24 months postvaccination. Based on Cochran test, there was no significant difference ($p$=0.135). The seroconversion rate for 12-14 years old age group was 87.5% at 3 months. Mumps IgG was detected in 81.3% and 87.5% at 12 months and 24 months post-vaccination respectively.

This difference was not statistically significant ($p$=0.717). Two subjects developed parotiditis and fever, 7-31 days following vaccination and were confirmed by serology.[4] The seroconversion rate was 86.1% (31/36) at 3 months following vaccination, while this rate remained positive in 77.8% (28/36) and 80.6% (29/36) after one and two years respectively ($p$=0.247). IgM seropositivity was 0%, 17% and 3% at the time of vaccination, 3 months and 12 months following vaccination respectively and based on Cochran test, the change was significance ($p$=0.006). Among 20 persons aged 6-11 years old, 2 seronegative IgM persons at the time of vaccination remained IgM positive in 3 months (IgM2) and one year (IgM3) following vaccination ($p$=0.135), but among 4 persons of 12-14 years old, one person remained positive at 12th month (IgM3) ($p$=0.039).

Based on sex (gender), there was no significant difference for IgM3 ($p$=0.389), but there was a difference for IgM2 of male and female ($p$=0.024), so that IgM2 was positive more in males than females at 3 months following vaccination. Based on the Fisher Exact test, no significant difference was noticed for age and these tests ($p$= 0.374 for age and IgM2 and $p$=0.444 for age and IgM3). Review of IgG at each section of study showed a 86.1% (31/36) seroconversion at 3 months following vaccination, of these seroconverted persons (28/31, 90.3%) remained seropositive and immune at 24th month following vaccination.

Review of reaction of IgG during 2 years period of study showed that among 36 seronegative IgG persons, seronegativity was as follows: 14% (5/36) due to vaccine failure at 3rd month while became seronegative in 3/36 (8%) at one year and 1/36(3%) at 24th month following vaccination.

Based on gender, there was no significant difference for IgG2, IgG3 and IgG4 ($p$>0.99) based on Fisher Exact test. In fact, the rate of Immunogenicity and efficacy of the Hoshino strain of mumps (included in MMR vaccine) against mumps in Shahr-e-Kord, Iran was reported to be 80.6% (29/36), 2 years after vaccination.

## Discussion

Since early Iranian calendar year of 1383 (20th March 2004), the MMR vaccination was introduced in national vaccination program. This vaccine contains Hoshino strain of mumps. In Iran, there is not report about the persistency of antibodies against this strain yet. In fact, the main purpose of this study was to determine the persistent mumps antibodies up to two years after MMR vaccination, in national vaccination program, so that to clear if any booster vaccine is needed in future. But a matter of question is that, it is not clear why the present age groups (12 months and 4–6 years old) were selected for mumps vaccination in Iranian EPI. One reason may be the convenience of the simultaneous administration of measles and rubella. Our first study found a seronegativity rate of 19.8%, which is lower than the rates reported in previous Iranian studies (34.2% and 29.4%),[1,2] but similar to the rate reported in Izmir, Turkey (20.1%).[5] However, wide discrepancies can occur like the Turkish study that reported a rate of only 10.9%.[6] In our first (screening) part of study, the age specific seropositive rate rose rapidly from 66.7% at age 7-11 years to 79.2% at age 12-14 years and 95.4% at age 15–18 years. The rate of individuals in a population with doubtful protection (unvaccinated, non-responder and low responder after primary vaccination) prevented to reach the herd immunity of 95% necessary for elimination of an infectious disease. [7] In the normal population, there was a herd immunity against infection, which was acquired by either natural infection, or by vaccination. Any vaccination program must have a high seroconversion rate accompanied by long time persistency to keep this herd immunity of 95%. There are some controversial reports about the antibodies

persisted against mumps. A study showed antibody in human subjects persisted without substantial decline for 8 years after mumps vaccination (Jeryl Lynn strain), for 5 years after measles-mumps-rubella and mumps-rubella combined vaccines, and for 2 years after measles-mumps vaccines, the longest periods tested.[8] Another study showed that seroconversion rate, magnitude of antibody titers, and incidence of clinical reactions following the trivalent vaccination include mumps Hoshino strain were similar to those occurring after the monovalent mumps Hoshino strain vaccination.[9] Sometimes persistence of antibodies depends on the viral strain. A study reported that children given MMR vaccine containing the Urabe mumps strain were less likely to be antibody negative than those given the Jeryl Lynn mumps strain (39/266, 15% vs 39/204, 19%, $p$=0.048).[10] A study on seroconversion and two vaccine protocol reported that in seronegative vaccines, the seroconversion rate was 86%. The antibody levels fell rapidly within the first year of follow-up, but remained relatively stable in subsequent years. After revaccination, the seropositivity rate was 95% and declined more slowly thereafter to 86% at year 9 of follow-up. The mean antibody titer was significantly ($p$<0.05) higher 4 years after the second MMR vaccination when compared with the corresponding time point after the first vaccination.[11] But sometimes the age affect the seronegativity. The levels of antibody against measles, mumps, and rubella were determined at 5-6 years postimmunization in 468 children vaccinated with two different trivalent vaccines. The proportions of children without detectable antibody levels were 12 and 3.6% for measles ($p$<0.001), 14.9 and 7% for mumps ($p$=0.006), and 3.3 and 3.1% for rubella ($p$=0.88), respectively, in MMR II and Trivirix recipients. A higher proportion of those vaccinated at younger ages had undetectable or low levels of measles antibody. These data indicate that a large proportion of children vaccinated under routine conditions did not have detectable measles and mumps antibody.[12] Also a study indicated that some seronegative persons may be due to primary vaccination failures.[3] In conclusion, the persistency of antibodies may be dependent on the monovalent or trivalent[8,9] mumps strain[10] or time point after the first vaccination,[1] which can vary with age of person.[12,13] Our first screening study showed that 338 patients (19.8%) were seronegative against mumps.[3] These seronegative persons were vaccinated with current MMR vaccine of Iranian national program. There was a seroconversion rate of 86% in our second study (three month post vaccination). Although there was a relatively a high rate of immunity against mumps strain, but later reduction in persistence antibodies within next years, resulted to level of immunity below 95% rate of herd immunity which was needed to eradicate mumps.

This study reported a 86% seroconversion rate following post-vaccination of Hoshino strain of mumps (included in MMR). The vaccine failure was about 14% and although 86% were seroconverted immediately post-vaccination immunity, but they waned and only 75% of children remained immune at the 24 months follow-up. Thus, one forth of children was susceptible to mumps. This is in line with the Ministry of Health and Education of Iran strategy to conduct a nationwide survey to confirm this level of immunity, and to change the strain of mumps included in MMR vaccine of Iran.

In the case of confirmation of such finding in next larger studies, it could be suggested to another booster dose of mumps vaccine in children vaccination very soon (for example 1-2 months) after vaccination (due to 14% vaccine failure) or two years after first vaccination (due to decreasing level of immunity to 75% at this time).

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**Conflict of interest:** None declared.

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Table 1: The complete data for persons by age, sex, school and Ig Profiles.*

| No | Age | Sex | IgM1 | IgM2 | IgM3 | IgG1 | IgG2 | IgG3 | IgG4 |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 9 | F | 0.20 | 0.41 | 0.29 | 0.24 | 2.4 | 2.45 | 4.50 |
| 2 | 9 | F | 0.20 | 0.23 | 0.19 | 0.38 | 2.12 | 1.95 | 4.30 |
| 3 | 13 | M | 0.21 | 1.45 | 3.19 | 0.27 | 3.06 | 2.67 | 4.90 |
| 4 | 8 | F | 0.21 | 0.47 | 0.35 | 0.31 | 2.44 | 2.24 | 4.30 |
| 5 | 13 | F | 0.22 | 0.34 | 0.32 | 0.15 | 1.18 | 0.69 | 3.05 |
| 6 | 10 | M | 0.22 | 1.9 | 0.69 | 0.19 | 2.26 | 3.08 | 4.45 |
| 7 | 13 | F | 0.22 | 0.29 | 0.26 | 0.34 | 1.91 | 1.47 | 2.75 |
| 8 | 12 | M | 0.22 | 0.34 | 0.23 | 0.52 | 2.02 | 1.75 | 2.60 |
| 9 | 9 | F | 0.26 | 0.34 | 0.28 | 0.55 | 2.23 | 2.27 | 2.95 |
| 10 | 8 | F | 0.27 | 0.32 | 0.28 | 0.11 | 2.88 | 3.6 | 5.35 |
| 11 | 13 | F | 0.28 | 067 | 0.46 | 0.22 | 2.21 | 1.85 | 3.20 |
| 12 | 13 | F | 0.28 | 0.48 | 0.47 | 0.24 | 2.58 | 2.27 | 3.46 |
| 13 | 13 | F | 0.28 | 0.46 | 0.38 | 0.45 | 2.15 | 1.99 | 4.24 |
| 14 | 9 | F | 0.3 | 0.62 | 0.45 | 0.17 | 1.9 | 1.75 | 3.17 |
| 15 | 8 | F | 0.36 | 0.38 | 0.33 | 0.17 | 1.8 | 0.56 | 0.32 |
| 16 | 8 | F | 0.36 | 0.44 | 0.48 | 0.41 | 2.12 | 1.29 | 1.96 |
| 17 | 12 | M | 0.38 | 1.16 | 0.6 | 0.2 | 1.79 | 1.86 | 2.94 |
| 18 | 9 | F | 0.38 | 0.30 | 0.35 | 0.85 | 1.43 | 1.35 | 2.17 |
| 19 | 14 | M | 0.39 | 0.65 | 0.52 | 0.12 | 1.1 | 1.1 | 5.15 |
| 20 | 10 | M | 0.39 | 0.56 | 0.49 | 0.25 | 3.11 | 2.79 | 3.89 |
| 21 | 10 | M | 0.39 | 0.52 | 0.45 | 0.91 | 2.04 | 1.85 | 2.13 |
| 22 | 12 | M | 0.41 | 0.71 | 0.59 | 0.14 | 2.17 | 1.88 | 3.08 |
| 23 | 14 | M | 0.43 | 0.84 | 0.75 | 0.65 | 1.2 | 1.15 | 4.80 |
| 24 | 8 | F | 0.46 | 0.61 | 0.59 | 0.18 | 2.38 | 1.75 | 3.14 |
| 25 | 9 | F | 0.47 | 1.15 | 0.84 | 0.61 | 2.87 | 2.46 | 3.17 |
| 26 | 13 | F | 0.51 | 0.78 | 0.59 | 0.73 | 2.41 | 1.9 | 2.65 |
| 27 | 10 | M | 0.52 | 0.28 | 0.27 | 0.44 | 1.11 | 1.10 | 0.49 |
| 28 | 9 | F | 0.53 | 0.78 | 0.68 | 0.54 | 2.44 | 2.22 | 3.98 |
| 29 | 9 | M | 0.55 | 1.04 | 0.91 | 0.27 | 2.2 | 2.05 | 2.67 |
| 30 | 13 | M | 0.57 | 1.67 | 0.75 | 0.3 | 1.6 | 2.66 | 0.56 |
| 31 | 12 | F | 0.77 | 0.83 | 0.79 | 0.27 | 12.6 | 10.4 | 4.67 |
| 32 | 13 | M | 0.78 | 1.24 | 1.04 | 0.44 | 4.12 | 3.82 | 4.01 |
| 33 | 8 | F | 0.65 | 0.77 | 0.54 | 0.28 | 0.45 | 0.52 | 0/43 |
| 34 | 13 | F | 0.37 | 0.47 | 0.48 | 0.23 | 0.70 | 0.61 | 0.82 |
| 35 | 8 | F | 0.30 | 0.34 | 0.30 | 0.39 | 0.71 | 0.41 | 0.56 |
| 36 | 8 | M | 0.18 | 0.23 | 0.19 | 0.55 | 0.79 | 0.51 | 0.48 |

elow to 0.9 is considered as negative value and more than> or =1 as positive value.
ıd IgG1 belong to the date of vaccination. IgM2 and IgG2 belong to the date of 3 months after vaccination.
ıd IgG3 belong to the date of one year after vaccination. IG4 belongs to the date of two year after vaccination.